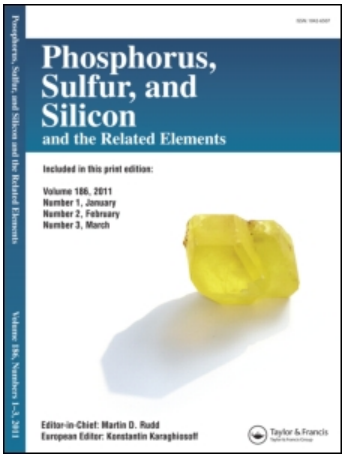

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HETEROCYCLIC COMPOUNDS STUDIES, SYNTHESIS OF 1,5-BENZOXATHIEPINES

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HETEROCYCLIC COMPOUNDS STUDIES, SYNTHESIS OF 1,5-BENZOXATHIEPINES

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1,5-Benzoxathiepinic derivatives have been obtained in good yields by the reaction of epichlorohydrines with 2-hydroxybenzenethiols in an aqueous alkalinic hydroxides medium. Their structures have been determined by ^{13}C NMR spectroscopy.

INTRODUCTION

In previous works it has been noted that 2-hydroxybenzenethiol is a suitable substrate to synthetize benzocondensed five- or six-membered heterocyclic rings containing oxygen and sulphur atoms. In fact, 2-hydroxybenzenethiol reacts with aldehydes, ketones, alkynes and halogenated esters bearing β-aryl or β-carboxyl groups to yield 1,3-benzoxathiolic derivatives[1,2]; on the other hand, when it is allowed to react with halogenated esters containing β-alkyl groups, 1,4-benzoxathianes are obtained.[3,4]

We now extend our research to the reaction between 2-hydroxybenzenethiol derivatives and epichlorohydrines with the aim to verify the possibility of obtaining either 1,4-benzoxathianic or 1,5-benzoxathiepinic derivatives. Despite their probable pharmacological properties, very few reports about the latter compounds have appeared in the literature.[5,6]

RESULTS AND DISCUSSION

Reactions have been carried out by treating equimolar amounts of 2-hydroxybenzenethiols (**1–3**) with epichlorohydrins (**4–8**) in an aqueous alkalinic medium (Scheme 1). From the reaction of (**1**) with (**4**), it has been possible to isolate 3-hydroxy-1,5-benzoxathiepine (**9**), as the sole product, without any detectable amount of the 1,4-benzoxathianic derivative. These results are in contrast with those obtained in the reactions of 1,2-benzodiols with epichlorohydrins, where mixtures of 1,4-benzodioxanes and 1,5-benzodioxepines are formed, with much higher yields of the benzodioxane derivatives.[7]

The stronger nucleophilic power of the thiophenoxide anion[8,9] can rationalize the formation of the 1,5-benzoxathiepinic derivative on the basis of a primary attack of

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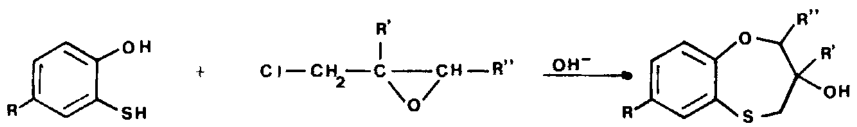


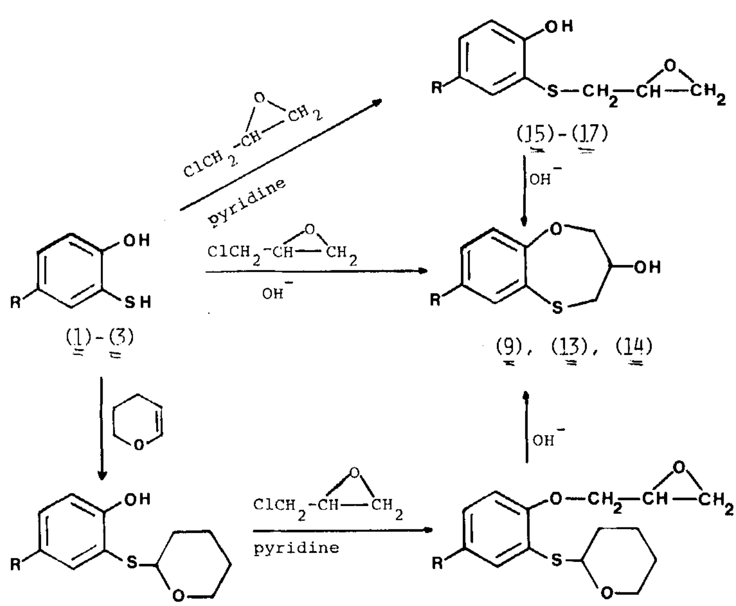
R = H	(1)
R = CH_3	(2)
R = Cl	(3)

R' = R'' = H	(4)
R' = H, R'' = CH_3	(5)
R' = C_2H_5, R'' = H	(6)
R' = H, R'' = C_6H_5	(7)
R' = C_6H_5, R'' = H	(8)

R = R' = R'' = H	(9)
R = R' = H, R'' = CH_3	(10)
R = R'' = H, R' = C_2H_5	(11)
R = R' = H, R'' = C_6H_5	(12)
R = CH_3, R' = R'' = H	(13)
R = Cl, R' = R'' = H	(14)

this ion on the carbon atom 3 of the eipchlorohydrin with formation of the epoxidic intermediate (**15**). A second nucleophilic attack by the phenoxide ion at the epoxidic carbon 1 yields 3-hydroxy-1,5-benzoxathiepine (**9**). We confirmed our hypothesis by isolating the epoxide (**15**) when carrying out the reaction in the presence of pyridine; a facile conversion of (**15**) to (**9**) was obtained by treatment with alkaline hydroxides (Scheme 2). The same results are always obtained if, after protecting the thiol group, the primary attack is performed by the phenoxide ion instead of the thiophenoxide one (Scheme 2).

To verify if this reaction could be directed towards the formation of 1,4-benzoxathianic derivatives, we examined the reactional behavior of epichlorohydrins (**5–8**)



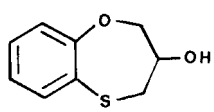
(1), (9), (15), (18), (19) R = H
(2), (13), (16) R = CH_3
(3), (14), (17) R = Cl

substituted in the one or two positions of the epoxidic moiety either by alkyl or aryl groups. By reaction of the compounds (**5–7**), we obtained selectively the 1,5-benzoxathiepinic derivatives (**10–12**), while we were not able to draw any conclusion in the case of (**8**). The isolated product did not give interpretable ^{1}H or ^{13}C NMR spectra, in spite of an elemental analysis and a molecular ion in perfect agreement with a six- or seven-membered ring structure. In fact, we performed both ^{1}H and ^{13}C NMR spectra in different solvents (namely deuteriochloroform and dimethyl-d_6 sulfoxide), at various temperatures (R.T., below −30°C and above +120°C), using three different NMR spectrometers with different magnetic fields (EM 360 L, FT 80 A, XL 100 Varian instruments) with always the same results, that is broad envelopes of bands which allowed us barely to distinguish between the aliphatic and the aromatic regions. We can rule out the presence of paramagnetic impurities, because of the very good resolution always observed for the tetramethylsilane line.

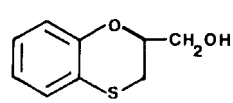
We obtained also the seven-membered heterocyclic ring performing the condensation reaction on 5-substituted 2-hydroxybenzenethiols (**2–3**), both directly or after isolating the epoxidic intermediates (**16–17**).

A comparison of the results obtained for 1,2-benzodiols[7] with those given by 2-hydroxybenzenethiols suggest that the larger sulphur atomic radius, causes the attack to occur at the terminal carbon atom, rather than at the central one, of the epoxidic moiety.

In order to establish which cycle, the 1,4-benzoxathianic or the 1,5-benzoxathiepinic one, had been actually formed in the case of the derivative (**9**), we decided to use ^{13}C NMR spectroscopy, with the aid of shift reagents. In fact, doping a deuteriochloroform solution of (**9**) with increasing amounts of $Yb(dpm)_3$, it was possible to observe a down-field variation of 15.5 Hz of the chemical shift, after the last addition of $Yb(dpm)_3$, of the signal at δ 68.75 ppm, versus minor variations for the signals at δ 75.97 ppm and δ 38.61 ppm, of 4.0 Hz and 4.3 Hz respectively. The signal which leads to the greater variation must be that which is responsible for the complexation site of the shift reagent. With a novel solution, again in deuteriochloroform, of (**9**), we obtained a fully proton coupled ^{13}C NMR spectrum, exhibiting a doublet feature (^{1}J = 141.5 Hz) for the signal at δ 68.75 ppm and two triplets for the other two signals, with ^{1}J = 138.5 Hz and ^{1}J = 142.3 Hz respectively. This spectral set of data is in agreement only with a benzoxathiepinic structure.



(9)



Similarly, we determined the structures for (**13**) and (**14**) derivatives.

In the case of (**11**), doping with shift reagents, it has been shown that the quaternary aliphatic carbon was the one bearing the OH group; it demonstrates, also in this case, the presence of a seven-membered heterocyclic structure. As for compounds (**10**) and (**12**), the spectral multiplicity (doublet) would have been the same for both structures, namely the benzoxathiepinic or benzoxathianic one, we based this on a former result obtained for (**9**). In fact, it had been noticed that, for the

signals of C-2 and C-4, after $Yb(dpm)_3$ doping, the variation of chemical shift was identical. Performing a similar experiment, e.g. for **(12)**, the maximum shift variation for C-3 was 144.9 Hz, whilst for C-2 and C-4 it was 110.2 Hz and 112.6 Hz, respectively. Such behavior is not compatible with a six-membered ring for the heterocyclic part of the molecules, but we must have again a benzoxathiepinic structure.

The dynamic behavior and the preferred conformation of the 1,5-benzoxathiepines are, at the moment, still under examination, as well as the possibility of synthesizing other similar heterocyclic system and will be the subject of future reports.

EXPERIMENTAL

The ^1H NMR spectra were determined in deuteriochloroform on a Varian FT 80 A spectrometer using tetramethylsilane as internal reference. ^{13}C NMR spectra were obtained in deuteriochloroform using the same instrument operating at 20 MHz at room temperature in the Fourier transform mode both under conditions of complete proton-noise decoupling as well as in the fully proton coupled mode. IR spectra were recorded on a Perkin–Elmer 157 G spectrophotometer using potassium bromide discs or neat liquids between sodium chloride plates. Mass spectra were measured with a "Hitachi" Perkin–Elmer RMU-6D spectrometer at 70 eV. Microanalyses were carried out on a Carlo Erba model 1106 Elemental Analyzer. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected.

Starting materials. 3-Chloro-1,2-epoxypropane **(4)** was a commercial product (Aldrich Chemical Company). 2-Hydroxybenzenethiol **(1)**, 5-methyl- **(2)** and 5-chloro-2-hydroxybenzenethiol **(3)**, 1-chloro-2,3-epoxybutane **(5)**, 2-ethyl- **(6)**, 1-phenyl- **(7)** and 2-phenyl-3-chloro-1,2-epoxypropane **(8)** were prepared by reported methods.[11–14]

General preparation of the 1,5-benzoxathiepines (9–14). A mixture of 2-hydroxybenzenethiol derivative **(1–3)** (0.1 mol), epichlorohydrin derivative **(4–7)** (0.1 mol) and 10% aqueous sodium hydroxide (0.12 mol) was refluxed with stirring for 15 hours, cooled and extracted with chloroform. The chloroform extracts were washed with 5% aqueous sodium hydroxide and water, then dried with sodium sulphate and solvent evaporated.

3-Hydroxy-1,5-benzoxathiepine (9). This compound was crystallized from ethanol:water = 1:1; mp 78°C. Yield: 80%. IR (KBr): 3300 (OH) cm^{-1}; ^{13}C NMR: δ 160.9 (s, C-10), 132.4, 129.0, 124.0, 122.3 (C-6, C-7, C-8, C-9, interchangeables), 128.4 (s, C-11), 75.9 (t, ^1J = 142.3 Hz, C-2), 68.7 (d, ^1J = 141.5 Hz, C-3) and 38.6 ppm (t, ^1J = 138.5 Hz, C-4). Molecular ion: m/e 182 (calcd. 182). Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.20; H, 5.59; S, 17.71.

2-Methyl-3-hydroxy-1,5-benzoxathiepine (10). This compound was chromatographed on a silica gel column using benzene:chloroform = 1:1 as eluent; mp 47–48°C. Yield: 58%. IR (KBr): 3380 (OH) cm^{-1}; ^{13}C NMR: δ 159.5 (C-10), 127.3, 125.6, 121.6, 118.4 (C-6, C-7, C-8, C-9, interchangeables), 122.5 (C-11), 78.2 (C-3), 75.7 (C-2), 68.7 (C-4) and 18.5 ppm (CH_3). Molecular ion: m/e 196 (calcd. 196). Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.17; S, 16.33. Found: C, 61.05; H, 6.08; S, 16.25.

3-Ethyl-3-hydroxy-1,5-benzoxathiepine (11). This compound was chromatographed on a silica gel column using chloroform as eluent; n_D^{30} 1.6035. Yield: 55%. IR (neat): 3350 (OH) cm^{-1}; ^{13}C NMR: δ 160.6 (s, C-10), 132.2, 128.9, 123.9, 122.1 (C-6, C-7, C-8, C-9, interchangeables), 128.5 (s, C-11), 79.2 (t, ^1J = 142.5 Hz, C-2), 72.7 (s, C-3), 42.1 (t, ^1J = 138.0 Hz, C-4), 29.7 (t, ^1J = 127.8 Hz, CH_2—CH_3) and 7.1 ppm (q, ^1J = 134.2 Hz, CH_2—CH_3). Molecular ion: m/e 210 (calcd. 210). Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.61; S, 15.25. Found: C, 62.69; H, 6.55; S, 15.14.

2-Phenyl-3-hydroxy-1,5-benzoxathiepine (12). This compound was crystallized from ethanol:water = 1:1; mp 93–94°C. Yield 75%. IR (KBr): 3350 (OH) cm^{-1}; ^{13}C NMR: δ 158.5 (s, C-10), 137.5–121.3 (aromatic), 75.0 (d, ^1J = 146.2 Hz, C-3), 74.5 (t, ^1J = 146.5 Hz, C-4) and 53.4 ppm (d, ^1J = 143.9 Hz, C-2). Molecular ion: m/e 258 (calcd. 258). Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.61; H, 5.38; S, 12.29.

7-Methyl-3-hydroxy-1,5-benzoxathiepine (13). This compound was chromatographed on a silica gel column using benzene:chloroform = 1:1 as eluent; n_D^{24} 1.6120. Yield: 63%. IR (neat): 3400 (OH) cm^{-1}. ^{13}C NMR: δ 158.7 (C-10), 133.1, 128.1 (C-7, C-11, interchangeables), 132.2, 129.0, 121.5 (C-6, C-8, C-9, interchangeables), 75.4 (C-2), 65.3 (C-3), 37.9 (C-4) and 20.2 ppm (CH_3). Molecular ion: m/e 196 (calcd. 196). Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.17; S, 16.33. Found: C, 61.09; H, 6.10; S, 16.21.

7-Chloro-3-hydroxy-1,5-benzoxathiepine (14). This compound was chromatographed on a silica gel column using benzene:chloroform = 1:1 as eluent; n_D^{24} 1.6290. Yield: 65%. IR (neat): 3400 (OH) cm^{-1}; ^{13}C

NMR: δ 158.4 (C-10), 131.0, 128.1, 122.7, (C-6, C-8, C-9, interchangeables), 129.2, 125.8 (C-7, C-11, interchangeables), 75.4 (C-2), 65.2 (C-3) and 37.5 ppm (C-4). Molecular ion: m/e 216 (calcd. 216). Anal. Calcd. for $C_9H_9ClO_2S$: C, 49.88; H, 4.19; S, 14.80. Found: C, 50.00; H, 4.08; S, 14.68.

Reaction of 3-chloro-2-phenyl-1,2-epoxypropane (8) with 2-hydroxybenzenethiol (1). The same procedure above described was followed. The product was purified by washing with diisopropyl ether; mp 92–94°C. Yield 53%. IR (KBr): 3450 (OH) cm^{-1}. For ^1H and ^{13}C NMR spectra see text. Molecular ion: m/e 258 (calcd. 258). Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.58; H, 5.35; S, 12.31.

General preparation of 3-[(2-hydroxyaryl)thio]-1,2-epoxypropanes (15–17). To a stirred mixture of 2-hydroxybenzenethiol derivative (**1–3**) (0.1 mol), pyridine (0.1 mol) and water (30 ml) 3-chloro-1,2-epoxypropane (**4**) (0.1 mol) was added dropwise at room temperature. After stirring for almost 8 hours at room temperature, the mixture was extracted with chloroform. The chloroform extracts were washed with water, dried with sodium sulphate and solvent evaporated.

3-[(2-Hydroxyphenyl)thio]-1,2-epoxypropane (15). This compound had $bp_{0.6}$ 164–165°C; n_D^{30} 1.6055.

Yield: 85%. IR (neat): 3400 (OH), 1245 (C—C) cm^{-1}; ^1H NMR: δ 7.10 (m, 4 H, Ar—H), 6.80 (s, 1 H, OH, D_2O exchanged), 3.71 (m, 1 H, S—CH_2—CH—CH_2), 3.49 (m, 2 H, S—CH_2—CH—CH_2) and 2.80 ppm (m, 2 H, S—CH_2—CH—CH_2). Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.19; H, 5.48; S, 17.48.

3-[(2-Hydroxy-5-methylphenyl)thio]-1,2-epoxypropane (16). This compound had $bp_{1.5}$ 134–136°C; n_D^{22}

1.6030. Yield 72%. IR (neat): 3350 (OH), 1240 (C—C) cm^{-1}; ^1H NMR: δ 6.94 (m, 3 H, Ar—H), 6.70 (s, 1 H, OH, D_2O exchanged), 3.81 (m, 1 H, S—CH_2—CH—CH_2), 3.53 (m, 2 H, S—CH_2—CH—CH_2), 2.88 (m, 2 H, S—CH_2—CH—CH_2) and 2.20 ppm (s, 3 H, Ar—CH_3). Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16; S, 16.33. Found: C, 61.10; H, 6.12; S, 16.21.

3-[(2-Hydroxy-5-chlorophenyl)thio]-1,2-epoxypropane (17). This compound had $bp_{0.1}$ 160–162°C; n_D^{22}

1.6175. Yield 68%. IR (neat): 3400 (OH), 1255 (C—C) cm^{-1}; ^1H NMR: δ 7.05 (m, 3 H, Ar—H), 6.75 (s, 1 H, OH, D_2O exchanged), 3.80 (m, 1 H, S—CH_2—CH—CH_2), 3.55 (m, 2 H, S—CH_2—CH—CH_2) and 2.90 ppm (m, 2 H, S—CH_2—CH—CH_2). Anal. Calcd. for $C_9H_9ClO_2S$: C, 49.88; H, 4.19; S, 14.80. Found: C, 49.79; H, 4.13; S, 14.68.

General method for the conversion of 1,2-epoxypropanes (15–17) to 1,5-benzoxathiepines (9, 13, 14). A mixture of 1,2-epoxypropane derivative (**15–17**) (0.02 mol) and 10% aqueous sodium hydroxide (0.02 mol) was refluxed with stirring for almost 8 hours, cooled and worked up in the same manner above described to furnish the compounds (**9**), (**13**), (**14**) in 84%, 87% and 78% yield, respectively. The IR and NMR spectra and melting points were identical with those of the above products.

Preparation of 1,2-epoxypropane derivative (19). To a stirred mixture of 2-[(tetrahydro-2H-pyran-2-yl) thio]phenol (**18**)[15] (0.044 mol), pyridine (0.044 mol) and water (10 ml), 3-chloro-1,2-epoxypropane (**4**) (0.044 mol) was added dropwise at room temperature. The resulting mixture was worked up in the same manner described for the preparation of (**15**). Yield 55%; bp_{22} 180–181°C; n_D^{20} 1.5920. ^1H NMR: δ 7.20

(m, 4 H, Ar—H), 4.40 (m, 2 H, O—CH_2—CH—CH_2), 4.10 (m, 1 H, S—CH—O), 3.80 (m, 1 H,

O—CH_2—CH—CH_2), 3.50 (m, 4 H, S—CH—O—CH_2—CH_2— and O—CH_2—CH—CH_2) and 1.60 ppm (m, 6 H, O—CH_2—CH_2—CH_2—CH_2). Anal. Calcd. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; S, 12.04. Found: C, 63.05; H, 6.74; S, 11.95.

Conversion of derivative (19) into 3-hydroxy-1,5-benzoxathiepine (9). (**19**) (0.01 mol) and 10% aqueous sodium hydroxide (0.01 mol) was refluxed with stirring for almost 24 hours. After cooling the mixture was worked up in the same manner described for the preparation of (**9–14**), to furnish (**9**) in 51% yield. The compound isolated from this reaction was identical to an authentic sample obtained above (mixed mp, IR and NMR data).

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